DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

m3208n

Food and Drug Administration
Center for Biologics Evaluation
and Research
1401 Rockville Pike
Rockville MD 20852-1448

CBER-00-006

NOV 24 1999

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Dr. Jean-Claude Vincent-Falquet
Director, Scientific Affairs
Pasteur Merieux Serums et Vaccins
58 Avenue LeClerc
Lyon, France 69007

Dear Dr.Vincent-Falquet:

The Food and Drug Administration (FDA) conducted an inspection of your manufacturing facility located at 1541 Avenue Marcel Merieux, Marcy L'Etoile, France, between July 19 and August 5, 1999. During the inspection, our inspectors documented significant deviations from the applicable standards and requirements of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and Title 21 Code of Federal Regulations (21 CFR), Parts 211 and 600-680 as follows:

1. Failure to establish separate or defined areas or other control systems for manufacturing and processing operations to prevent contamination or mix-up [21CFR 211.42(c) and 600.11] in that after sterile filling, partially stoppered vials are covered with wipes, stored for up to ——————— and loaded into the lyophilizer located in the Class ——— filling suite. Furthermore, these vials are exposed to a Class ——— area when the operator opens the other side of the lyophilizer to place thermocouples into product vials. During these activities, there is no assurance that sterile filled products such as Rabies Vaccine and Haemophilus Vaccine are maintained in an aseptic environment until vial stoppering is completed.

2. Failure to establish and follow control procedures to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product [21 CFR 211.110(a)] in that:

a. There is no in-process or lot release specification for ——— used in the purification of Tetanus toxin during the manufacture of Act-HIB ® and for residual ——— used during the manufacture of Typhoid Vi Polysaccharide Vaccine.

b. The sterile connection and blending operations steps of all vaccine bulk concentrates and sterile buffer have not been validated.

c. There are no mixing studies for U.S. licensed products.

3. Failure to ensure that reprocessed batches will conform with all established standards, specifications, and characteristics [21 CFR 211.115(a) and 211.110(a)] in that there is no written procedure and validation data that supports the re-filtration of —— following a failed sterility test.

4. Failure to establish appropriate written procedures designed to prevent microbial contamination of drug products purporting to be sterile and to assure that such procedures include validation of any sterilization processes [21 CFR 211.113(b)] in that not all interventions that occur during the manufacturing process are simulated during aseptic media fills.

5. Failure to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity [21 CFR 211.160(b)] in that:

a. Bacteriostasis and fungistasis test has not been performed for all filled products and bulk drug substance concentrates. [21 CFR 610.12]

b. Flushing of points of use immediately prior to sampling is not representative of production use.

c. There are no established minimum temperature standards for the depyrogenation oven used to sterilize and depyrogenate glass vials.

d. No test method validation studies have been performed for ——— content in Typhoid Vaccine and ——— content in Rabies Vaccine.

6. Failure of the quality control unit to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. Additionally, you failed to submit error and accident reports to CBER [21 CFR 211.22, 211.192, and 211.194(a)(8)(e) and 21 CFR 600.14(a)]. For example:

a. Typhim Vi lot P0323 failed Vi polysaccharide content at the ——— stability time-point; however, the test result was reported as pass by Quality Control. No investigation was performed.

b. The residual moisture and reconstitution time tests at the ——— stability time-point for Rabies Vaccine lot M0475 were either not performed or not documented and no investigation was performed.

c. Rabies Vaccine lots N0018 and M0162 failed potency test at ——— stability time-points respectively; however, no investigation was performed and an error and accident report was not submitted to CBER.

7. Failure to establish adequate written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess [21 CFR 211.100(a)] in that your written procedure entitled "Nonconformity Control" allows for a second test to be performed for an out of specification test result without conducting an investigation as to the cause of the out of specification result [21 CFR 211.192]. For example:

a. Typhim Vi lot P0482 failed ———content at the ——— stability time-point and although the test was considered valid, a second test was performed without an investigation.

b. Thymoglobulin lot TH002 failed the test for ——— and although the test was considered valid, a second test was performed without an investigation and the lot was released based on the second test result.

8. Failure to clean, maintain, and sanitize equipment and utensils at appropriate intervals to prevent malfunction or contamination that would alter the safety, identity, strength, quality, or purity of the drug product [21 CFR 211.67(a) and 600.11(b)] in that:

a. Not all sterilizing filters have been validated for microbial retention, extractables, and compatibility.

b. Not all vent filters are integrity tested after use.

c. The effectiveness of the sanitizers used to clean filling equipment has not been established.

d. Cleaning validation studies have not been performed on all multi-use and dedicated equipment.

9. Failure to assure that the equipment used in the manufacture, processing, packing, or holding of a drug product is of appropriate design and adequate size for its intended use [21 CFR 211.63] in that the flexible water lines used for the water for injection and purified water supply to the vial washer create a deadleg when not in use.

We acknowledge receipt of your response dated September 15, 1999, to the Form FDA 483 issued at the close of the inspection. Corrective actions addressed in your letter may be referenced in your response to this letter, as appropriate. Our evaluation of your response follows, and is numbered to correspond to the items listed on the Form FDA 483:

2a. We acknowledge your commitment to discontinue the use of the ——wipes, the transport of partially stoppered vials through a Class ——area, and the storage of partially stoppered vials in a cold room. Please provide a time frame for the implementation of the above referenced commitment.

In addition, the response indicated that changes to your facility to ensure that filling, stoppering, unloading sterile vials, storage of filled vials, and loading vials into the freeze dryer are performed in a Class — environment ———————— ———— However, it is our view that your proposed completion time period is excessive given the potential for impact on product quality associated with your operations and the absence of validation and control systems necessary to prevent contamination. Please provide a revised completion date for the validation or additional justification. Any additional justification should not rely solely on passing final release specifications as the basis of your response.

2b. We acknowledge your commitment to revise your media fill procedure to better reflect the manufacturing conditions and to include the interventions identified during the inspection in the next schedule media fill. Please provide the completion date for the next schedule media fill, a copy of your revised media fill procedure, and any interim controls to ensure a high sterility assurance level.

5a. The response indicated that ———————— ———— Please note that the if ———— is performed in the future, the ———— procedures must be validated and submitted as a prior approval supplement to your license.

7. Please clarify whether the vent filter replacement program for —— and air supply lines includes vent filter post-use integrity testing.

8b. Please provide a copy of your revised procedure entitled "Monitoring of the efficacy of manual cleaning of the filling equipment building ——including the tests methods and acceptance criteria.

Neither this letter nor the list of inspectional observations (Form FDA 483) is meant to be an all-inclusive list of deviations. It is your responsibility to ensure that your facility is in compliance with the provisions of the Federal Food, Drug, and Cosmetic Act and all applicable regulations.

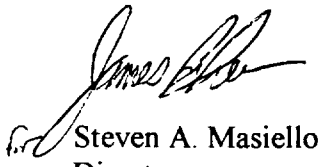
You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Such actions include license suspension and/or revocation. Federal agencies are advised of the issuance of all Warning

Letters about drugs and devices so that they may take this information into account when considering the award of contracts.

You should notify this office in writing, within 15 working days of receipt of this letter, of any additional specific steps you have taken to correct the noted deviations and to prevent their recurrence. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your reply should be sent to the following address: Mr. Steven A. Masiello, Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448.

Sincerely,



Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and
Research